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Replacing hormone therapy—is the decline in prescribing sustained, and are nonhormonal drugs substituted?

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Abstract

Objectives: After two cautioning landmark studies in 2002 and 2003, a dramatic decrease in hormonal therapy (HT) prescribing for menopausal symptoms was seen. Our objectives were to (1) determine whether this decline in HT prescribing sustained until 2007 and (2) investigate nonhormonal drug prescribing for women who stopped HT.

Methods: We analyzed drug dispensing data from community pharmacies in The Netherlands. For the first objective, we analyzed exposure prevalence of HT. For our second objective, we selected all women who were dispensed HT prescriptions between August 2002 and August 2003. From this study cohort, we defined our index group as all women who stopped HT shortly after the studies (n = 1,254) and a reference group as all women who continued HT (n = 839). We calculated the incidence of nonhormonal therapies for both groups, reporting risk ratio (RR) and 95% CI. Kaplan-Meier curves were also constructed.

Results: Mean exposure prevalence of HT (per 1,000 women) pre 2002 versus post 2004 was 30.6 versus 15.3 (50.0% decline) for 40 to 49 years, 79.2 versus 25.5 (67.7% decline) for 50 to 59 years, and 28.4 versus 11.6 (59.1% decline) for 60 to 69 years. HT exposure remained low until 2007. HT stoppers receive more clonidine, RR 3.48 (2.36-5.13); anxiolytics or sedatives, RR 1.46 (1.15-1.87); and osteoporosis prophylaxis and treatment, RR 2.04 (1.14-3.66). Young stoppers (40-49 y) received more antidepressants, RR 2.70 (1.41-5.11), whereas older stoppers (60-69 y) received less antidepressants, RR 0.43 (0.18-1.05). Kaplan-Meier curves showed that nonhormonal drug prescribing occurred soon after HT was stopped.

Conclusions: This study shows the dramatic and sustained impact of the cautioning landmark studies on HT prescribing. HT stoppers received more nonhormonal therapies for menopausal symptoms compared with those who continued HT.

Key Words: Hormone therapy – Menopause – Prescribing – Psychotropic drugs.

Hormone therapy (HT) has been used for many years to alleviate menopausal symptoms.[1] In 1998, the Heart and Estrogen/Progestin Replacement Study (HERS) concluded that HT offered no protection for cardiovascular events in postmenopausal users with established coronary disease.[2] Still, a 2001 review concluded that HT was effective in reducing menopausal symptoms, portrayed only minimal risks for hormone-related cancer (primarily breast cancer), and reduced the risk for cardiovascular disease.[3]

Two landmark studies, the Women Health Initiative (WHI) trial in July 2002[4] and the observational Million Women Study (MWS) in August 2003,[5] reported severe adverse effects of HT. The increased risk for breast cancer was confirmed, but more novel, HT was found to significantly increase the risk for coronary heart disease, pulmonary embolism, and stroke.[4,5] In the public[6] as well as professional opinion,[7,8] these risks of HT outweighed their benefits.

In The Netherlands and most other countries, after the cautioning publications and the subsequent media and professional attention, a dramatic decrease in HT prescribing occurred. This decline, as demonstrated by earlier studies from our group, was most pronounced in the younger age categories, and in The Netherlands, a larger decline was seen after publication of the MWS in 2003 compared with the WHI trial in 2002.[9,10]

The decline in HT prescribing has led to an increased interest in nonhormonal therapies for improving menopausal symptoms.[7] Several treatment modalities can be prescribed for this aim. Two meta-analyses found moderate efficacy in the treatment of vasomotor symptoms with clonidine, gabapentin, and selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs).[11,12] Another meta-analysis found that mood disorders and depression during menopause could be effectively treated with several antidepressant drug classes, including tricyclic antidepressants, SSRIs, and SNRIs, although effectiveness

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might be dependent on age.[13] Sleep disorders are commonly treated with a broad range of psychotropic drugs, primarily anxiolytics and sedatives.[14] Nonhormonal prophylaxis and treatment of postmenopausal osteoporosis include bisphosphonates and calcium and vitamin D supplementation.[15] Use of over-the-counter medication, including complementary and alternative medicine, is relatively common among postmenopausal women.[16]

The first objective of this study was to determine whether the decline in HT prescribing in The Netherlands was sustained up until the end of 2006. There is no explicit reason to suspect that the downward trend in HT has changed since 2003.[9] However, reversals in drug-prescribing trends have been described previously. Furthermore, the Dutch association of gynecologists Nederlandse Vereniging voor Obstetrie en Gynaecologie (NVOG) and the Dutch association of general practitioners (Nederlands Huisartsen Genootschap [NHG]) still maintain, albeit with caution, menopausal symptoms as an indication for HT.[17,18] Our second objective was to investigate nonhormonal drug prescribing in women who stopped HT shortly after the publication of the MWS results in August 2003—the study that evoked the largest decline in HT prescribing in The Netherlands.[9] We hypothesized that nonhormonal drug prescribing for menopausal symptoms in these women would be increased compared with women who continued HT use.

METHODS

Database

We analyzed drug dispensing data from Dutch community pharmacies using IADB, which holds prescription records of approximately 500,000 individuals (www.IADB.nl).[19,20] In the IADB, each prescription record contains basic patient characteristics (anonymous identifier, gender, and date of birth) and medication information on drug name, anatomical therapeutical chemical code, dosage, and dispensing date. Commitment of people to their pharmacy has been shown to be high in The Netherlands,[21] ensuring complete medication histories of individuals. Prescription data between 2002 and 2006 were used for the analyses. Focusing on our two study objectives, we determined exposure prevalence of HT, based on *prevalence* analyses, and nonhormonal therapy substitution, based on *incidence* analyses.

Exposure prevalence of HT

We analyzed monthly exposure prevalence of HT between 2000 and 2007. Population data were obtained from the Dutch Central Bureau of Statistics. To assess the effect of the cautioning publications, namely, (1) the WHI trial in July 2002[4] and (2) the MWS in August 2003,[5] the publication dates of these studies were indicated. We performed time-trend analyses to determine whether the decline in HT prescribing was significant. The regression models

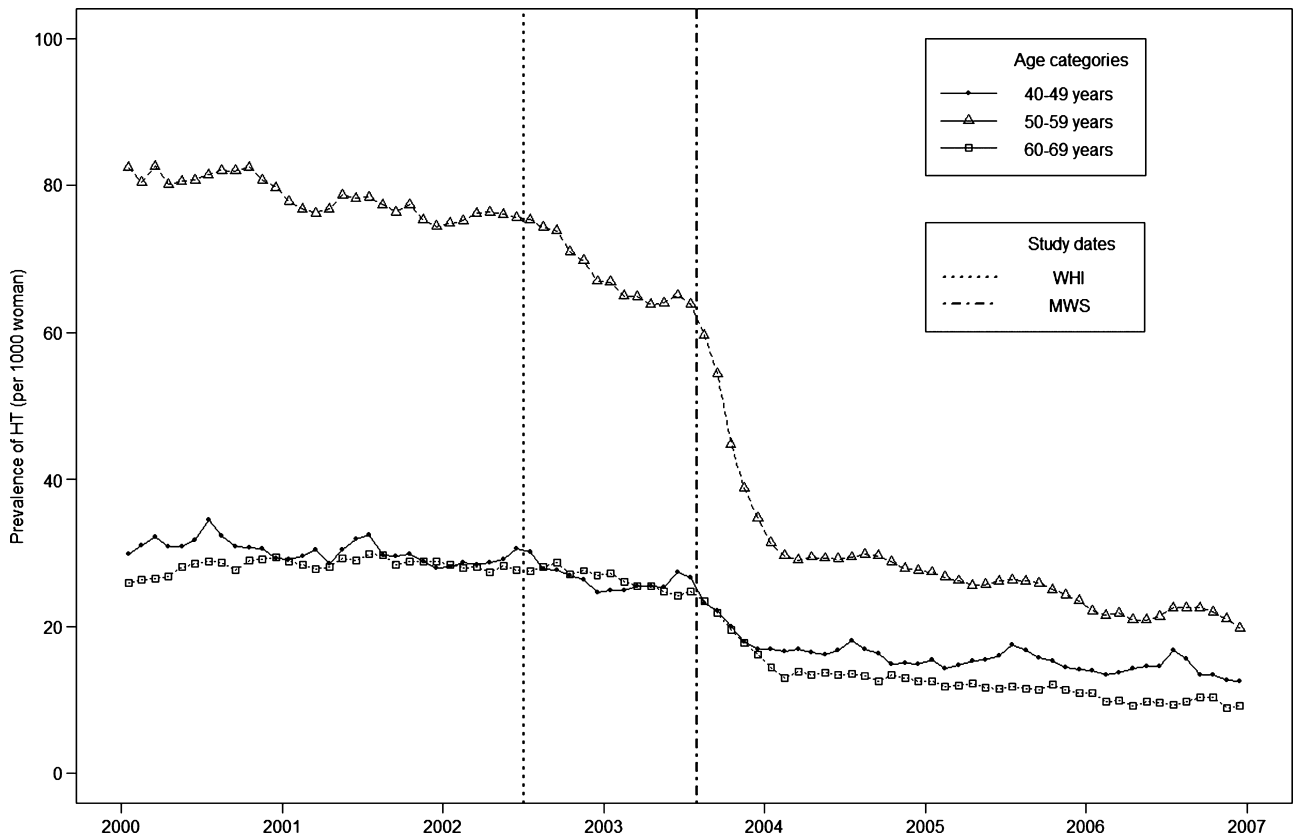

FIG. 1. Monthly exposure prevalence of HT, stratified per age category. Publication dates of the two landmark studies are marked with vertical lines. HT, hormone therapy; WHI, Women's health Initiative; MWS, Million Women Study.

included a constant term, a term for linear time trend, and a binary indicator to indicate HT prescribing from before the WHI trial versus after the MWS (thus measuring the decline in HT prescribing).[22]

HT and nonhormonal therapy

For this study, we defined HT to constitute estrogen plus progestogen therapy, estrogen-only therapy, progestogen-only therapy, and the synthetic hormone tibolone. All formulations were included (oral, transdermal, injections, nasal, implant, and depot), except vaginal preparations containing estradiol or estriol, as these are regarded to be without any risk.[5] Nonhormonal therapies were selected to include the following drug classes: (1) clonidine, (2) gabapentin, (3) antidepressants, (4) anxiolytics and sedatives, (5) antipsychotics, and (6) osteoporosis prophylaxis and treatment. Prescription records in our data set did not include data on OTC medication, including complementary and alternative medicine, and we were therefore unable to include these in our analyses.

Study population, index, and reference group

We selected all women aged 40 to 69 years on January 1, 2003, from the IADB. We included only the individuals known in the database since August 2002 and been dispensed at least one HT prescription between August 2002 and August 2003. From this study population we selected all women who stopped HT between August 2003 and January 2004 (index group) and all women who continued HT at least until July 2004 (reference group). Stopping was defined as not receiving a prescription for HT for at least 3 months after the stop date of the last HT prescription. Women, who according to this definition, stopped before August 2003 or between January 2004 and July 2004, were excluded, although they could later again receive prescriptions of HT. Finally, women lacking enough follow-up time (less than 12 months) were excluded.

Analyses

The end date of the last HT prescription was chosen as the starting point for follow-up in the index group. The mean stop date was subsequently used as the starting point for follow-up in the reference group. The incidence rate of drug prescribing was calculated as the number of incident cases divided by the total number of patient-days.[23] Number of patient-days was measured from the starting point for follow-up up until either the prescription date of the nonhormonal drug, the last known date of that person in the database, or the end of the study period, whichever occurred first. When calculating the incidence rate of nonhormonal drug prescribing, women who were dispensed this drug 1 year before their starting point for follow-up were not considered, because these women were not at risk to receive this drug. For example, in the analysis of antidepressant use, we did not consider women who were prescribed antidepressants up to 1 year before their starting point for follow-up; other nonhormonal drug classes, however, were allowed to be prescribed. We compared the index and reference groups and calculated incidence risk ratio (IRR) and 95% CI.[23] We performed subanalyses per age category (40-49 y, 50-59 y, and 60-69 y) and, where appropriate, per specific type of drug. Univariate survival analysis was performed by determining Kaplan-Meier (KM) curves. All statistical analyses were performed using R, version 2.5.1.[24]

TABLE 1. *Population at risk (n), incident cases (Cases), incidence rate (per 100.000 patient-days), and incidence risk ratio (IRR) with 95% confidence intervals (95% CI) for the different nonhormonal treatment classes*

	Index (HT stoppers) (total n = 1,254)			Reference (HT continuers) (total n = 839)			
Treatment class	n	Cases	Incidence rate	n	Cases	Incidence rate	IRR (95% CI)
Clonidine							
Overall	1,201	143	17.4	816	31	5.0	3.48 (2.36-5.13)
Gabapentin							
Overall	1,247	12	1.3	830	11	1.7	0.76 (0.34-1.73)
Antidepressants							
Overall	1,046	108	14.5	671	54	10.8	1.34 (0.97-1.86)
Specific drug							
TCA	1,046	59	7.7	671	28	5.5	1.40 (0.89-2.20)
SSRI	1,046	43	5.6	671	19	3.7	1.51 (0.88-2.60)
Other	1,046	22	2.8	671	14	2.7	1.04 (0.53-2.03)
Age category							
40-49 y	274	34	17.8	262	13	6.6	2.70 (1.42-5.11)
50-59 y	646	66	14.3	328	29	11.8	1.21 (0.78-1.88)
60-69 y	126	8	8.6	81	12	20.0	0.43 (0.18-1.05)
Anxiolytics and sedatives							
Overall	839	196	36	558	97	24.6	1.46 (1.15-1.87)
Antipsychotics							
Overall	1,232	8	0.9	819	6	0.9	1.00 (0.35-2.88)
Osteoporosis prophylaxis and treatment							
Overall	1,184	45	5.1	791	15	2.5	2.04 (1.14-3.66)
Specific drug							
Bisphosphonates	1,184	29	3.3	791	8	1.3	2.54 (1.16-5.55)
Calcium	1,184	32	3.6	791	10	1.6	2.25 (1.11-4.58)
Vitamin D	1,184	1	0.1	791	3	0.5	0.20 (0.02-1.92)

HT, hormone therapy; TCA, tricyclic antidepressant; SSRI, selective serotonin reuptake inhibitor.

A P value of less than 0.05 was deemed to be statistically significant.

RESULTS

Exposure prevalence of HT

Monthly exposure prevalences of HT are shown in Fig. 1. The decline in exposure prevalence was modest after publication of the WHI trial 4, especially for women aged 40 to 49 years and 60 to 69 years. However, a large decline can be observed in all age categories following publication of the MWS.[5] Exposure prevalence remained low from 2004 until the end of 2006. Mean exposure prevalence (per 1,000 women) of HT pre 2002 versus post 2004 was 30.6 versus 15.3 (50.0% decline) for women aged 40 to 49 years, 79.2 versus 25.5 (67.7% decline) for 50 to 59 years, and 28.4 versus 11.6 (59.1% decline) for 60 to 69 years. Time-trend analysis showed that HT prescribing from before the WHI trial versus after the MWS was significantly reduced in all age categories ($P < 0.001$).

Nonhormonal drug prescription

Selection of study population

The IADB held records of 100,523 women aged 40 to 69 years on January 1, 2003, and known in the database since August 2002. Of those women, we selected all who were dispensed HT prescriptions between August 2002 and August 2003, resulting in a total population of 5,721 women eligible for the study.

Selection of index and reference groups

Our index group comprised 1,254 women who stopped their HT use between August 2003 and January 2004. Our

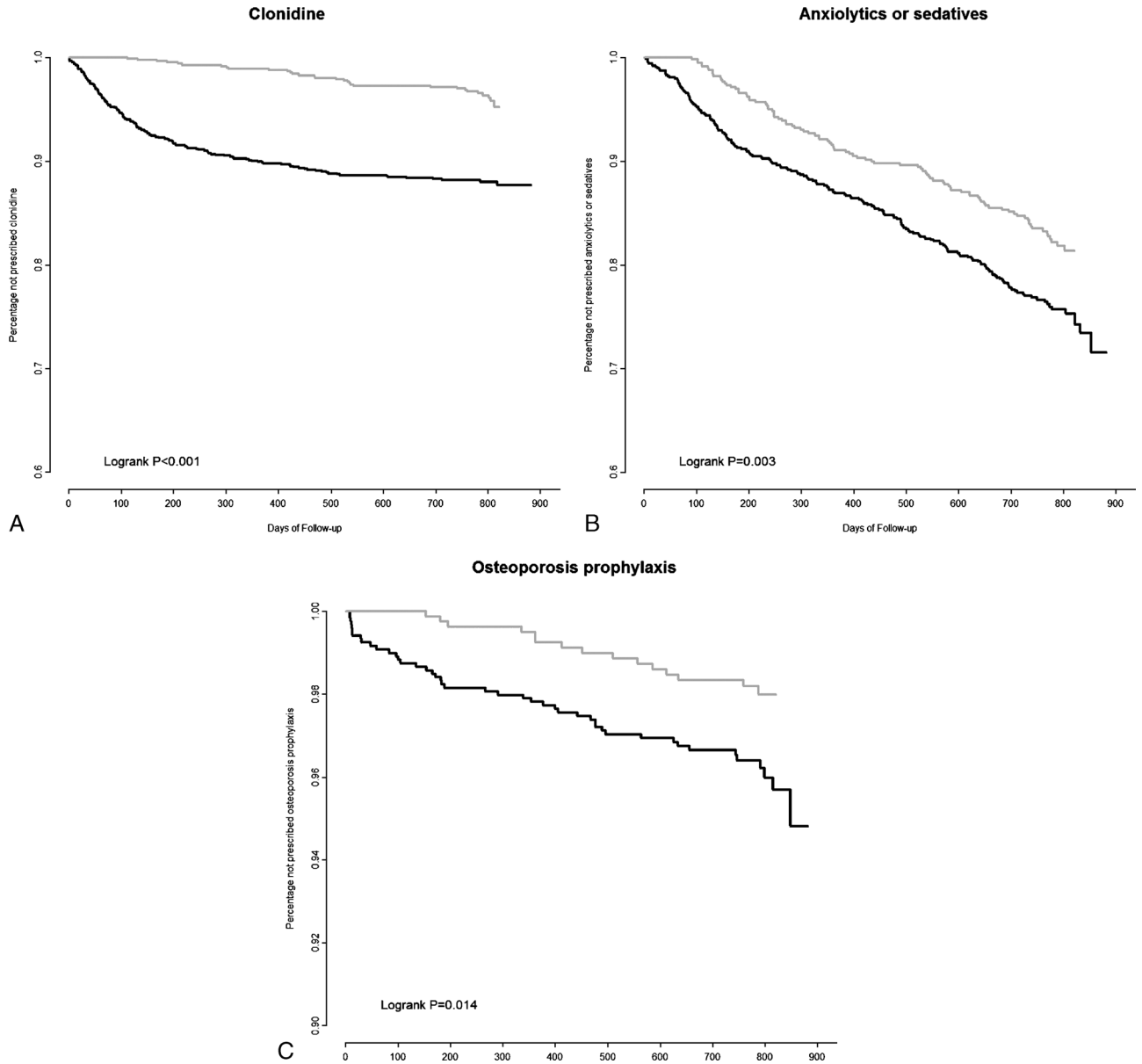

FIG. 2. Time to nonhormonal drug prescription for patients who stopped HT (solid line) or continued HT (gray line). **A**: clonidine; **B**: anxiolytics or sedatives; **C**: osteoporosis prophylaxis. HT, hormone therapy.

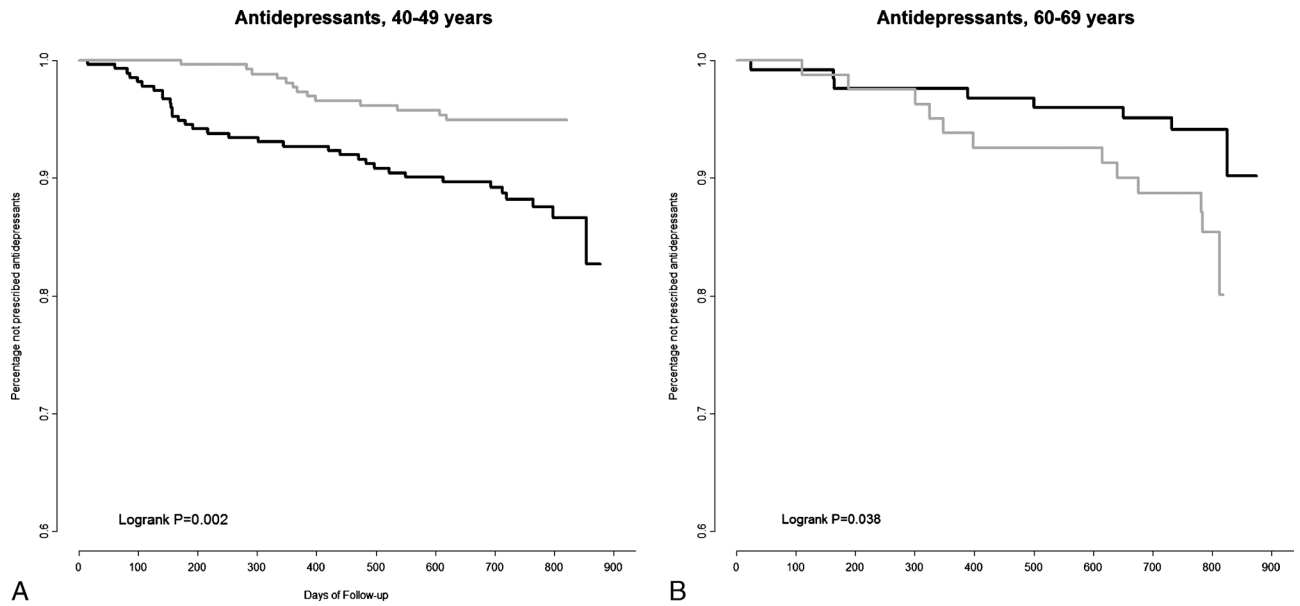

FIG. 3. Time to antidepressant prescription for patients who stopped HT (solid line) or continued HT (gray line). **A**: 40-49 years; **B**: 60-69 years.

reference group consisted of 839 women who continued HT use at least until July 2004. Other women in the study population were excluded for reason of stopping before August 2003 (n = 2,954), stopping between January 2004 and July 2004 (n = 379), or lacking sufficient follow-up time (n = 295). Mean age in the index group was 53.9 (SD 5.7) years; mean age in the reference group was 53.1 (SD 6.6) years. The difference in age between groups was significant ($P < 0.01$) but not considerable.

Prescription of nonhormonal drugs

Population at risk, number of incident cases, incidence rate (per 100.000 patient-days), and IRR with 95% CI are presented for the nonhormonal drug classes in Table 1. Also shown are subanalyses per age category for antidepressants and per specific type of drug for antidepressants and osteoporosis prophylaxis and treatment.

Nonhormonal drug prescribing in the index group differed significantly with the reference group for several drug classes, including clonidine (IRR 3.48, 95% CI 2.36-5.13), anxiolytics and sedatives (IRR 1.46, 95% CI 1.15-1.87), and osteoporosis prophylaxis and treatment (IRR 2.04, 95% CI 1.14-3.66). Overall IRR of antidepressants was borderline significant (IRR 1.34, 95% CI 0.97-1.86), while overall IRRs of gabapentin and antipsychotics did not reach statistical significance.

Point estimates of the IRR in most drug classes did not differ considerably by age category (data not shown except for antidepressants). In the antidepressant class, however, a significantly increased incidence rate for the index group was found in the age category 40 to 49 years (IRR 2.70, 95% CI 1.41-5.11). Conversely, in the age category 60 to 69 years the incidence rate for the index group was decreased, albeit borderline significant (IRR 0.43, 95% CI 0.18-1.05).

Antidepressant use was increased for both tricyclic antidepressants and SSRIs, but not for the other types of antidepressants (including SNRIs and monoamine oxidase inhibitors). The incidence rate for osteoporosis medication was only increased for bisphosphonates (IRR 2.54, 95% CI 1.16-5.55) and calcium supplements (IRR 2.25, 95% CI 1.11-4.58).

KM curves were plotted for all drug classes; significance of the log-rank *P* values corresponded with the significance of the IRRs for all drug classes. Shown in Figure. 2 are KM curves for clonidine, anxiolytics and sedatives, and osteoporosis prophylaxis. These KM curves suggest that prescribing occurs soon after stopping HT. Shown in Figure. 3 are KM curves for antidepressants, paneled for age categories 40 to 49 years and 60 to 69 years. The difference in antidepressant prescribing is significant and opposite between the two age categories.

DISCUSSION

Time-trend analysis on HT prescribing

In agreement with previous studies by our group,[9,10] we found a dramatic and statistically significant decline in exposure prevalence of HT after publication of the MWS. This study shows that HT prescription is continuously low from 2004 up until the end of 2006, confirming that the decline is sustained. Compared to the decline following the MWS, the decline following the WHI trial was modest. Other countries have described a decline in HT prescribing following the WHI trial, including Australia,[25] Canada,[26,27] Ireland,[28] New Zealand,[29] the United Kingdom,[30] and the United States.[31-33] Only one of these studies analyzed data beyond 2004, which also reported the sustained impact on HT prescribing.[33] The response to the MWS is much less reported in literature. This could be because unlike in the

Netherlands, the WHI trial had already portrayed a considerable effect on HT prescribing in most countries, obscuring an additive effect of the MWS. Still, the Irish study reported that the decline in HT prescribing after the WHI trial sustained after the MWS.[28]

Nonhormonal drugs prescription

Women who stopped HT use shortly after the publication of the MWS in August 2003 were more often prescribed nonhormonal drugs indicated for treatment of menopausal symptoms, confirming our hypothesis. Incidence of clonidine, antidepressants (in the age category 40-49 y), anxiolytics and sedatives, and osteoporosis prophylaxis and treatment were all significantly increased in women who stopped HT compared with women who continued HT. Survival plots showed that these nonhormonal drugs are prescribed soon after HT cessation. A US study reported that approximately half of all women who stopped HT developed vasomotor, urogenital, or mood-related disorders.[32] The study also found that 60% of all patients with menopausal symptoms were treated with nonhormonal therapy, primarily antidepressants of the SNRI class.[32] An Irish study showed an increase in the prescription rate of bisphosphonates correlating with a decrease in HT prescribing.[28]

The incidence of antidepressant prescribing for women stopping HT was significantly increased in the age category 40 to 49 years and borderline significantly decreased in the age category 60 to 69 years. This is in line with the conclusions of Cohen et al,[13] who found that perimenopausal depression in younger women can be effectively treated with estrogen therapy,[34] whereas hormonal treatment was not found to be effective in a trial with older women,[35] and those of Freeman et al,[36] who found that depressive symptoms increased during transition to menopause and decreased in postmenopausal women.

While performing the analyses for this study, we found a relatively large number of women prescribed both HT and antidepressant drugs. In 2003, antidepressant drug prevalence among women using HT was 14.6%, 17.1%, and 14.7% in women aged 40 to 49, 50 to 59, and 60 to 69 years, respectively. These prevalences were 11.0%, 11.4%, and 9.8% in the general population (all χ^2 $P < 0.001$), based on IADB data. These data suggest that a subgroup of women in the menopausal transition phase was not sufficiently treated with HT alone and needed a combination of antidepressants and HT. The "missed" symptoms of menopause, such as sleep disturbances, mood changes, and somatic complaints,[37] can play an important role. Further research is needed on this topic.

Limitations

For our analyses on nonhormonal drug prescribing, we used strict exclusion criteria. These ensured that our index group comprised only women who had consistently used HT up until the publication of the MWS, after which they stopped, whereas our reference group consisted only of women who were consistently prescribed HT at least up until July 2004. A possible limitation of these criteria is that knowledge of the results of the WHI trial, published in July 2002, may have influenced general practitioners' or women's behavior. However, in The Netherlands, media attention after the WHI was negligible,[9] and this study showed that influence on HT prescribing behavior was small compared with that of the MWS. If, alternatively, we had selected stoppers after the WHI trial, this could have introduced bias by including many women who did not stop HT because of their own or their general practitioner's concerns about the therapy but for unrelated reasons. Although our strict exclusion criteria may raise concerns over the generalizability of the results, they increase the internal validity of the study by accurately focusing on the women of interest.

Our data set consists of drug dispensing data from community pharmacies. We were therefore unable to include over-the-counter medication, including complementary and alternative medicine, in our analysis. This has probably led to an underestimation in the proportion of nonhormonal therapies started by women stopping HT. Further research, preferably interview based, is warranted to investigate the use of these treatment alternatives.

Our prescription database does not contain information on indications for drug use and type of prescriber. It would be interesting to study what drugs women with menopausal complaints without HT are being prescribed currently; data on indications for drug use, however, are a prerequisite for such a study.

Clinical implications

Although this is a descriptive study, we think that a clinical implication of this study is the concern for adverse effects associated with the increase in nonhormonal therapies. Recently, a randomized controlled trial in healthy postmenopausal women found that calcium supplementation was associated with an increased risk for cardiovascular events.[38] Other nonhormonal treatment modalities investigated in this study are not known for increased risk for cardiovascular event or cancer when used in therapeutic dosages. However, other types of adverse effects are well known, including fatigue, insomnia, nausea, and headaches.[39] An implication of this study is the recommendation for future research to assess whether the risk-benefit ratio of nonhormonal treatment modalities for menopausal complaints is superior to the HT used previously.

CONCLUSION

This study shows the dramatic and sustained impact of two cautioning landmark studies, the WHI trial and the MWS, on hormone therapy prescribing. HT stoppers recieved more nonhormonal therapies for menopausal symptoms compared to those who continued HT, including clonidine; anxiolytics or sedatives; and osteoporosis prophylaxis and treatment. Young stoppers (40-49 y) received more antidepressants, while older stoppers (60-69 y) recieved less antidepressants.

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